One Year Post Exclusivity Adverse Event Review: Atovaquone-Proguanil

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Background Drug Information

- **Drug:** Malarone® and Malarone Pediatric® (atovaquone-proguanil)
- **Therapeutic Category:** anti-malarial
- **Sponsor:** GlaxoSmithKline
- **Indication:** Treatment of *P. falciparum* malaria in patients ≥5 kg and prophylaxis in patients ≥11 kg
- **Original Market Approval:** July 14, 2000
- **Pediatric Exclusivity Granted:** August 6, 2003

Drug Use Trends in Outpatient Settings: Atovaquone-Proguanil

- Malarone® and Malarone Pediatric® accounted for roughly 5% and 0.2%, respectively, of the 3.7 million prescriptions dispensed for the antimalarial class in the U.S. (Aug 2003 to Jul 2004).[1]
- Dispensed prescriptions for Malarone Pediatric® increased roughly 34.5% from approximately 5,500 (Aug 2002 to Jul 2003) to over 7,300 (Aug 2003 – Jul 2004).[1]
- Pediatricians were responsible for roughly 4.3% (~7,800 prescriptions) of Malarone® and 40.4% (~2,900 prescriptions) of Malarone Pediatric® dispensed in the U.S. between August 1, 2003 and July 31, 2004.[1]

[1]IMS Health, National Prescription Audit *Plus*™, Moving Annual Totals, Aug 2001 – Jul 2004, Extracted Oct 2004

Pediatric Exclusivity Studies: Atovaquone-Proguanil

Malaria Treatment

- **Trial 1 (n=200):** Compared the safety and efficacy of atovaquone-proguanil to amodiaquine in the treatment of acute uncomplicated *P. falciparum* malaria in pediatric patients weighing 5-11 kg

- Result: Adequate clinical response was obtained in 95% of patients treated with atovaquone-proguanil versus 53% of patients treated with amodiaquine.

Pediatric Exclusivity Studies: Atovaquone-Proguanil

Malaria Prophylaxis Trials

- **Trial 2 (n=330):** A double-blind placebo-controlled study evaluating the safety and efficacy of atovaquone-proguanil in the prevention of *P. falciparum* malaria in an endemic area in pediatric patients weighing 11-40 kg
- Method: Patients with acute *P. falciparum* malaria were treated with artesunate and subsequently randomized to either atovaquone-proguanil or placebo for malaria prophylaxis.
- Result: <1% of patients treated with atovaquone-proguanil for prophylaxis had treatment failure versus 22% of untreated patients.

Pediatric Exclusivity Studies: Atovaquone-Proguanil

Malaria Prophylaxis Trials (continued)

- **Trial 3 (n=221):** An international, open label, randomized trial to compare atovaquone-proguanil to chloroquine-proguanil in the prevention of malaria in non-immune pediatric patients weighing 11-50 kg traveling to an endemic area

- Result: Study was not large enough to allow for statements of comparative efficacy

Labeling Changes Resulting from Exclusivity Studies

- Added pharmacokinetic clearance data as a function of body weight for pediatric patients ≥11 kg
- Extended labeling of atovaquone-proguanil down to 5 kg for the treatment of acute, uncomplicated *P. falciparum* malaria
- Added safety data for pediatric patients 5 to <11 kg who received atovaquone-proguanil for the treatment of acute uncomplicated *P. falciparum* malaria

Relevant Safety Labeling

- Pediatric Use- Most commonly reported adverse events attributable to atovaquone-proguanil:
  - Treatment of malaria (5- <11 kg): diarrhea
  - Treatment of malaria (11-40 kg): vomiting and pruritis
- Pediatric Use- Most commonly reported adverse events possibly attributable to atovaquone-proguanil or placebo:
  - Prophylaxis of malaria (≥11 kg): headache, fever and abdominal pain
- Other treatment emergent adverse events observed in pediatric studies of prophylaxis:
  - Abdominal pain & vomiting
  - Headache
  - Cough

Labeled Post-Marketing Adverse Events

- ***Skin:*** Cutaneous reactions ranging from rash, photosensitivity, and urticaria to rare cases of erythema multiforme and Stevens-Johnson syndrome
- ***Central Nervous System:*** Rare cases of seizures and psychotic events (such as hallucinations); however, a causal relationship has not been established

Adverse Event Reports since Market Approval: Atovaquone-Proguanil

07/14/00 – 09/06/04

- Total number of reports, all ages†*:
  - 293 reports (76 US)
    - 240 serious (37 US)
      - 6 deaths (0 US)
- Pediatric reports*:
  - 17 reports (3 US)
    - 15 serious (2 US)
      - 3 deaths (0 US) (2 unduplicated reports)

†Includes reports with unknown age

*Counts may include duplicate reports

Pediatric Deaths Prior to Post-Exclusivity Period (n=2) (Foreign Reports)

- **Both deaths occurred while on treatment for *P. falciparum* malaria**
  - 14 month old with severe anemia, three days presumed fever, and hepatosplenomegaly
    - Treated with chloroquine and paracetamol for two days
    - Parasite count of 733/200 WBC and hematocrit of 12%
    - Received two days of atovaquone-proguanil and became dyspneic with increasing anemia and severe hypoglycemia. Placed on oxygen and died before receiving blood transfusion
    - Death presumed to be due to severe malarial anemia and hypoglycemia but causal link to atovaquone-proguanil could not be excluded

Pediatric Deaths Prior to Post-Exclusivity Period (n=2) (Foreign Reports cont.)

- 22 month old with severe anemia, five days of presumed fever, anorexia, occasional vomiting and tachycardia
  - Treated with chloroquine and paracetamol for three days
  - Parasite count of 730/230 WBC and hematocrit of 14%
  - Received one dose of atovaquone-proguanil and subsequently patient deteriorated and died 45 minutes after the dose
  - Death presumed to be due to severe malarial anemia but causal link to atovaquone-proguanil could not be excluded

Adverse Event Reports during the One-Year Post-Exclusivity Period: Atovaquone-Proguanil
08/06/03 – 09/06/04

- Total number of reports, all ages[†*]:
  - 122 reports (40 US)
    - 89 serious (8 US)
      - No deaths
- Pediatric reports[*]:
  - 7 reports (3 US)
    - 6 serious (2 US)
      - No deaths

[†]Includes reports with unknown age

[*]Counts may include duplicate reports

Top 10 Reported Adult Adverse Events during the One-Year Post-Exclusivity Period

- Nausea
- Vomiting
- Abdominal Pain
- Headache
- Dizziness
- Insomnia
- Nightmares
- Pyrexia
- Fatigue
- Abortion spontaneous

Underlined events = Unlabeled events

Pediatric Adverse Events during the One-Year Post-Exclusivity Period

Unduplicated pediatric reports in patients on atovaquone-proguanil for malaria prophylaxis:

- 4 cases of allergic type reactions
  - Facial edema +fever
  - Blepharitis +drug ineffective +malaria
  - Drug hypersensitivity +pruritus +urticaria
  - Acute psoriaform reaction (AST and ALT increased)

Underlined events = Unlabeled events

Pediatric Adverse Events during the One-Year Post-Exclusivity Period (cont.)

- 16 yr. old on atovaquone-proguanil for 19 days for malaria prophylaxis
  - 1-2 days after completing malaria prophylaxis patient woke up with blurry vision and was “unable to see 3 inches”. Saw MD, ophthalmologist, and retinal specialist and was given prescription glasses. Reported by non-health professional who described this patient as being “legally blind”.
  - Ophthalmologist diagnosis was “Acute myopia possible drug effect”. Retinal specialist noted retinal striae in both eyes.
  - Resolved after one week

Summary: Pediatric Adverse Events

- Eye Disorders
  - Current labeling for atovaquone-proguanil derived from the results of an adult malaria prophylaxis trial lists “visual difficulties” in 2% of patients on atovaquone-proguanil versus 3% in patients on mefloquine.
  - Since marketing approval, there have been post-marketing AERS reports in adults of visual blurring (3), eye pain (2), eye swelling (2), and eye disorders (2).
- Hypersensitivity, including cutaneous reactions, has been addressed in current labeling.
- Elevation of transaminases associated with treatment of malaria have also been described in current labeling.

Summary: Atovaquone-Proguanil

- This completes the one-year post-exclusivity AE monitoring as mandated by BPCA.
- FDA recommends routine monitoring of AEs for this drug in all populations.
- Does the Advisory Committee concur?

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